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AB
6/12/98

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al. Atty Dkt. No.: 0701:027F

Serial No.: Unknown
Continuation of 08/691,604
Filed: August 15, 1996
Group Art Unit: 1205
Examiner: Henley III, R.

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)ALBUTEROL

To: Assistant Commissioner for Patents
Box PATENT APPLICATION
Washington, D.C. 20231

Preliminary Amendment Under 37 C.F.R. 1.115

Dear Sir;

Prior to examination, please amend the application as follows:

In the Title:

Please delete "METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)ALBUTEROL" and substitute therefor --METHOD FOR INDUCING BRONCHODILATION USING OPTICALLY PURE R(-)ALBUTEROL--.

In the specification:

Page 1, between line 2 and line 3, insert:

--Cross Reference to Related Applications

This application is a continuation of ~~our prior copending~~ application 08/691,604, filed August 15, 1996, which ~~was~~ is a now U.S. Patent 5,760,090,

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April 2, 1998

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continuation of application 08/335,480, filed November 7, 1994, now US patent 5,547,994, which was a continuation of application 08/163,581, filed December 7, 1993, now US patent 5,362,755, which was a continuation of application 07/896,725, filed June 9, 1992, now abandoned, which was a continuation of application 07/461,262, filed January 5, 1990, now abandoned.--

In the Claims:

Cancel claims 1-12.

Please add the following claims:

13. (New) A method of inducing bronchodilation or providing relief of bronchospasm, comprising administering to an individual a quantity of optically pure R-(-) albuterol sufficient to induce said bronchodilation.

14. (New) A method according to Claim 13, wherein the albuterol comprises at least 90% by weight of the R(-) isomer and not more than 10% by weight of the S(+) isomer.

15. (New) A method according to Claim 13, wherein the albuterol comprises at least 99% by weight of the R(-) isomer and 1% or less by weight of the S(+) isomer.

16. (New) A method according to Claim 13, wherein the optically pure R(-) albuterol is administered by inhalation.

17. (New) A method according to Claim 13, wherein the optically pure R(-) albuterol is administered in an amount of about 30 μg to about 90 μg.

18. (New) A method according to Claim 13, wherein the optically pure R(-) albuterol is administered orally.

19. (New) A method according to Claim 18, wherein the optically pure R(-) albuterol is administered in an amount of about 1 mg to about 8 mg.

20. (New) A method according to Claim 18, wherein the optically pure R(-) albuterol is administered as a syrup.

21. (New) A method according to Claim 13, wherein the optically pure R(-) albuterol is administered as a syrup.

22. (New) A method of inducing bronchodilation or providing relief of bronchospasm while reducing the concomitant liability of adverse effects associated with racemic albuterol, comprising administering to an individual a quantity of optically

pure R-(-) albuterol sufficient to induce said bronchodilation while simultaneously reducing said adverse effects.

REMARKS

The present application is a continuation of US application, serial number 08/691,604. Claims 1-12 were present in the application as filed. All claims pending in the original application are canceled by amendment above and are replaced by new claims. Claims 13-22 are therefore pending in this continuation application.

In the parent application, 08/691,604, claims were allowed to "a method of treating asthma". New claims 13-22 relate to "a method for inducing bronchodilation or providing relief of bronchospasms". Support for the new wording relating to inducing bronchodilation or providing relief of bronchospasms is found on page 5, line 5-6, page 3, line 8-9 and elsewhere in the specification. Applicants respectfully submit that new claims 13-22 are allowable with a terminal disclaimer for reasons of record in parent application 08/691,604.

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In order to expedite prosecution, Applicants enclose herewith terminal disclaimers in accordance with 37 CFR 1.321 (b) and (c) and fees under 37 C.F.R. 1.20(d).

Respectfully submitted,

Philip E. Hansen
Agent for Applicants
Reg. No. 32,700

Dated: April 21, 1998

Address for Correspondence:
Philip E. Hansen
Heslin & Rothenberg, P.C.
5 Columbia Circle
Albany, New York 12203
Telephone: (518) 452-5600
Facsimile: (518) 452-5579

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April 2, 1998

TERMINAL DISCLAIMER TO OBVIATE A PROVISIONAL DOUBLE PATENTING REJECTION OVER A PENDING SECOND APPLICATION	Docket No. 0701.02F

In re Application of: Barberich et al.
Application No. 09/063551
Filed: 04/21/98
For: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)-ALBUTEROL

16X · 5-15-98 Henley GR 16/96

The owner, SEPRACOR, INC. of 100.00 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173 as shortened by any terminal disclaimer filed prior to the grant of any patent granted on pending second Application Number 08/691,604, filed on August 15, 1996. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the second application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon grantee, its successors or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of any patent granted on the second application, as shortened by any terminal disclaimer filed prior to the patent grant, in the event that any such granted patent: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims cancelled by a reexamination certificate, is reissued, or in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

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Check either box 1 or 2, if appropriate.

1. ☐ For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney of record.

3. Owner/applicant is ☒ Small entity ☐ Large entity

The terminal disclaimer fee under 37 CFR 1.20(d) is $55.00 and is to be paid as follows:

☒ A check in the amount of the fee is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 08-1935. A duplicate copy of this sheet is enclosed.

PTO suggested wording for terminal disclaimer was

☒ unchanged. ☐ changed (if changed, an explanation should be supplied.)

Philip E. Hansen
Signature

Dated: April 21, 1998

Name and Address of Person Signing

Philip E. Hansen
Heslin & Rothenberg, P.C.
5 Columbia Circle
Albany, NY 12203
WILLARI 00000012 09063551
55.00 OP

I certify that this document and fee is being deposited on with the U.S. Postal Service as first class mail under 37 C.F.R. 1.8 and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Signature of Person Mailing Correspondence

Typed or Printed Name of Person Mailing Correspondence

P26/REV01

Terminal Disclaimer To Obviate A Double Patenting Rejection Over A Prior Patent			Docket No. 0701.027F
In Re Application Of: **Barberich et al.**			
Serial No.	Filing Date 04/21/98	Examiner	Group Art Unit
Invention: **METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)-ALBUTEROL**			
Owner of Record: **SEPRACOR, INC.**			

RECEIVED
MAY 11 1998
MATRIX CUSTOMER SERVICE CENTER

TO THE ASSISTANT COMMISSIONER FOR PATENTS:

The above-identified owner of record of a **100%** percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior Patent No. *5,547,994*. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors and/or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney of record.

Philip E. Hansen (signature) Dated: *April 21, 1998*

Signature

Philip E. Hansen

Typed or Printed Name

☒ Terminal disclaimer fee under 37 C.F.R. 1.20(d) included.
☒ PTO suggested wording for terminal disclaimer was unchanged.
☐ Certification under 37 C.F.R. 3.73(b) is required if terminal disclaimer is signed by the assignee.

04/24/1998 WILLBRI 00000032 09063823 ... FC:248

P32/REV01

Terminal Disclaimer To Obviate A Double Patenting Rejection Over A Prior Patent	Docket No. 0701.027F

In Re Application Of: **Barberich et al.**

Serial No.	Filing Date	Examiner	Group Art Unit
	04/21/98		

Invention: **METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)-ALBUTEROL**

RECEIVED

Owner of Record: **SEPRACOR, INC.**

MAY 1 1 1998

OMER

MATRIX CUSTOMER SERVICE CENTER

TO THE ASSISTANT COMMISSIONER FOR PATENTS:

The above-identified owner of record of a **100%** percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application, which would extend beyond the expiration date of the full statutory term defined in 35 U.S.C. 154 to 156 and 173, as presently shortened by any terminal disclaimer, of prior Patent No. **5,362,755** . The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors and/or assigns.

In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. 154 to 156 and 173 of the prior patent, as presently shortened by any terminal disclaimer, in the event that it later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ For submissions on behalf of an organization (e.g., corporation, partnership, university, government agency, etc.), the undersigned is empowered to act on behalf of the organization.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

2. ☒ The undersigned is an attorney of record.

Philip E. Hansen Dated: April 21, 1998

Signature

Philip E. Hansen

Typed or Printed Name

☒ Terminal disclaimer fee under 37 C.F.R. 1.20(d) included.

☒ PTO suggested wording for terminal disclaimer was unchanged.

☐ Power of attorney or certification under 37 C.F.R. 3.73(b) is required if terminal disclaimer is signed by the assignee.

04/1998 MTIL 00000012 08063551

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P32/REV01

SUBJECT: DECISION ON TERMINAL DISCLAIMER/ INFORMAL FORM

DATE: 6-15-98 APPL. S.N. 09/063,551

TO EXAMINER: R. Henley ART UNIT: 1614

M. MONTGOMERY ROOM 1E18 MAILROOM DATE 4-21-98

AFTER FINAL YES ____ NO ✓ NUMBER OF T.D(S). FILED 3

INSTRUCTIONS: I have reviewed the submitted T.D. with the results as set forth below. If you agree, please use the appropriate form paragraphs identified by this informal memo in your next office action to notify applicant about the T.D. If you disagree with my analysis or have questions at all about the acceptability of the T.D., please see me or your Special Program Examiner. THIS IS AN INTERNAL MEMO ONLY. IT MUST NOT BE MAILED TO APPLICANT. FOR STORAGE COPY TO BE IN DEPT IN FILE.

[✓] The T.D. is PROPER and has been recorded. (See 14.23).

[ ] The T.D. is NOT PROPER and has not been accepted for the reason(s) checked below. (See 14.24).

[ ] The recording fee of $_____ has not been submitted nor is there any pre authorization in the application file to charge to a deposit account. (See 14.26.07)

[ ] Application Examiner has not processed T.D. fee. (See fee authorization).

[ ] The T.D. does not satisfy Rule 321(b)(3) in that the person who has signed the T.D. has not stated his/her interest (and/or the extent of the interest of the business entity represented by the signature) in the application/patent. (See 14.26 and 14.26.01).

[ ] The T.D. lacks the enforceable only during the common ownership clause needed to overcome a double patenting rejection, Rule 321(c). (See 14.27, 14.27.01).

[ ] It is directed to a particular claims(s), which is not acceptable since "the disclaimer must be of a terminal portion of the term of the entire patent to be granted". MPEP 1490. (See 14.26, 14.26.02).

[ ] The person who signed the terminal disclaimer:
- [ ] has failed to state his/her capacity to sign for the business entity. (See 14.28).
- [ ] is not recognized as an officer of the assignee. (See 14.29 and possibly 14.29.01).

[ ] No documentary evidence of a chain of title from the original inventor(s) to assignee has been submitted, nor is the reel and frame specified as to where such evidence is recorded in the office. 37 CFR 3.73(b). (See 1140 O.G. 72). *NOTE:* This documentary evidence or the specifying of the reel and frame may be found in the T.D. or in a seperate paper submitted by applicant. (See 14.30).

[ ] No "statement" specifying that the evidentiary documents have been reviewed and that, to the best of the assignee's knowledge and belief the title is in the assignee seeking to take action. 37 CFR 3.73(b). (See 1140 O.G. 72) (See 14.31).

[ ] The T.D. is not signed. (See 14.26, 14.26.3). or 14.26.03 if TD is not signed by all the owners.

[ ] Attorney not of record in oath/decl. or a seperate paper filed appointing a new or associate attorney. (See 14.29.01).

[ ] The serial number of the application (or the number of the patent) which forms the basis for the double patenting is missing or incorrect. (See 14.32).

[ ] The serial number of this application (or the number of the patent in reexam or reissue case(s) being disclaimed is missing or incorrect. (See 14.26, 14.26.04 or 14.26.05).

[ ] The period disclaimed is incorrect or not specified. (See 14.27, 14.27.2 or 14.27.3)(For Samples 14.27.04 and 14.27.05)

[ ] Other: _____

[ ] Suggestion to request refund of $ _____. (See 14.35, 14.36).

[ ] EXAMINER NOTE: IF APPLICATION IS IN CONDITION FOR ALLOWANCE ANY OF THE ABOVE INFORMALTIES MAY BE FAXED IN TO THE GROUP

FOR SAMPLE TERMINAL DISCLAIMERS AND CERTIFICATES:

[ ] Sample of a TD over a pending application and assignee Certificate (See 14.37).
[ ] Sample of a TD over a prior patent and assignee Certificate (See 14.38).
[ ] Sample Assignee Certificate under 37 CFR 3.73 (b) (See 14.39)

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/063,551	04/21/98	BARBERICH T	0701.027F

HM42/0624

PHILIP E HANSEN
HESLIN & ROTHENBERG
5 COLUMBIA CIRCLE
ALBANY NY 12203

EXAMINER	
HENLEY III, R	
ART UNIT	PAPER NUMBER
1614	5

DATE MAILED: 06/24/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/98) U.S. GOVERNMENT PRINTING OFFICE 1998-411-518/40276 1- File Copy

DLEV011664

Notice of Allowability

Application No.	Applicant(s)
09/063,551	Timothy J. Barberich, et al.
Examiner	**Group Art Unit**
Ray Henley	1614

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course.

☒ This communication is responsive to *the papers filed April 21, 1998*.

☒ The allowed claim(s) is/are *13-22*.

☐ The drawings filed on _____ are acceptable.

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) _____.
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" of this Office action. Failure to timely comply will result in ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

☐ Applicant MUST submit NEW FORMAL DRAWINGS

- ☐ because the originally filed drawings were declared by applicant to be informal.
- ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review, PTO-948, attached hereto or to Paper No. _____.
- ☐ including changes required by the proposed drawing correction filed on _____, which has been approved by the examiner.
- ☐ including changes required by the attached Examiner's Amendment/Comment.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any response to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

- ☒ Notice of References Cited, PTO-892
- ☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 2
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152
- ☐ Interview Summary, PTO-413
- ☐ Examiner's Amendment/Comment
- ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
- ☐ Examiner's Statement of Reasons for Allowance

RAYMOND HENLEY, III
PRIMARY EXAMINER
GROUP 1200

Notice of References Cited

Application No.	Applicant(s)
09/063,591	Timothy J. Barberich, et al.

Examiner	Group Art Unit	Page 1 of 1
Ray Henley	1814	

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS
	A	5,760,090	6/2/98	Barberich et al.	514	649
	B	5,362,755	11/94	Barberich et al.	514	649
	C	5,547,994	8/96	Barberich et al.	514	649
	D					
	E					
	F					
	G					
	H					
	I					
	J					
	K					
	L					
	M					

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUBCLASS
	N						
	O						
	P						
	Q						
	R						
	S						
	T						

NON-PATENT DOCUMENTS

*		DOCUMENT (Including Author, Title, Source, and Pertinent Pages)	DATE
	U		
	V		
	W		
	X		

6/25/98

* A copy of this reference is not being furnished with this Office action. (See Manual of Patent Examining Procedure, Section 707.05(a).)

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

HM42/0624

PHILIP E HANSEN
HESLIN & ROTHENBERG
5 COLUMBIA CIRCLE
ALBANY NY 12203

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
09/063,551	04/21/98	010	HENLEY III, R	1614	06/24/98

First Named Applicant: BARBERICH, TIMOTHY J.

TITLE OF INVENTION: METHOD FOR INDUCING BRONCHODILATION USING OPTICALLY PURE R(-)ALBUTEROL (AS AMENDED)

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 0701.027F	514-649.000	F87	UTILITY	NO	$1320.00	09/2[illegible]/98

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status, or

B. If the status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

A. Pay FEE DUE shown above, or

B. File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

II. Part B-Issue Fee Transmittal should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B-Issue Fee Transmittal should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "4b" of Part B-Issue Fee Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give application number and batch number. Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PATENT AND TRADEMARK OFFICE COPY

PTOL-85 (REV. 10-96) Approved for use through 06/30/99. (0651-0033)

U.S. GPO: 1996-437-639/60023

DLEV011667

PART B - ISSUE FEE TRANSMITTAL

242 - 1660
Bal - 30

Complete and mail this form, together with applicable fees, to: Box ISSUE FEE
Assistant Commissioner for Patents
Washington, D.C. 20231

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE. Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Issue Fee receipt, the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

PHILIP E HANSEN
HESLIN & ROTHENBERG
5 COLUMBIA CIRCLE
ALBANY NY 12203

10/12/1624
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Publishing Division
SEP 08 1998
16

Note: The certificate of mailing below can only be used for domestic mailings of the Issue Fee Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing.

Certificate of Mailing

I hereby certify that this Issue Fee Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Box Issue Fee address above on the date indicated below.

Philip E. Hansen (Depositor's name)
(Signature)
September 3, 1998 (Date)

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
09/063,551	04/21/98	010	HENLEY III, R. 1614	06/24/98

First named inventor: BARBERICH, TIMOTHY J.

TITLE OF INVENTION: METHOD FOR INDUCING BRONCHODILATION USING OPTICALLY PURE R(-)ALBUTEROL (AS AMENDED)

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 0701.027F	514-649.000	F87	UTILITY	NO	$660.00 ~~$1660.00~~	09/24/98

Change of correspondence address or indication of "Fee Address" (37 CFR 1.363). Use of PTO form(s) and Customer Number are recommended, but not required.

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47) attached.

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 Heslin & Rothenberg
2
3

5. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)
PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the PTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Sepracor, Inc.

(B) RESIDENCE: (CITY & STATE OR COUNTRY) Marlborough, MA

Please check the appropriate assignee category indicated below (will not be printed on the patent)
☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fees are enclosed (make check payable to Commissioner of Patents and Trademarks):
☒ Issue Fee
☒ Advance Order - # of Copies 10

4b. The following fees or deficiency in these fees should be charged to:
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PTO UTILITY GRANT
Paper Number 6

The United States of America

The Commissioner of Patents and Trademarks

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this

United States Patent

Grants to the person(s) having title to this patent the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States of America or importing the invention into the United States of America for the term set forth below, subject to the payment of maintenance fees as provided by law.

If this application was filed prior to June 8, 1995, the term of this patent is the longer of seventeen years from the date of grant of this patent or twenty years from the earliest effective U.S. filing date of the application, subject to any statutory extension.

If this application was filed on or after June 8, 1995, the term of this patent is twenty years from the U.S. filing date, subject to an statutory extension. If the application contains a specific reference to an earlier filed application or applications under 35 U.S.C. 120, 121 or 365(c), the term of the patent is twenty years from the date on which the earliest application was filed, subject to any statutory extension.

Bruce Lehman
Commissioner of Patents and Trademarks

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PATENT SPECIFICATION

(11) 1,298,494

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(72) Inventor DAVID MIDDLEMISS

(54) PHENYLETHANOLAMINE DERIVATIVES

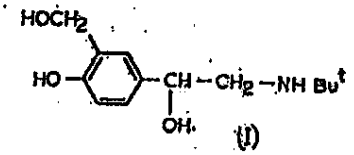
(71) We, ALLEN & HANBURYS LIMITED, a British Company of Three Colts Lane, Bethnal Green, London, E.2., do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with a process for the preparation of optical enantiomers of certain 1 - phenyl - 2 - aminoethanol derivatives which are described in particular in our United Kingdom Specification No. 1,200,886.

In our said United Kingdom Specification No. 1,200,886 there are described phenylaminoethanol derivatives which may stimulate β - adrenergic receptors e.g. α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^2 - diol (I). The practical utility of such activity is more fully described in said Specification.

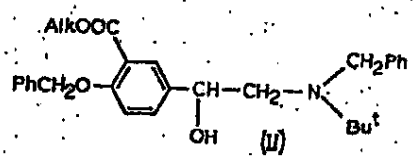
The phenylaminoethanol derivatives (I) may exist in two optically isomeric forms and according to the invention we have discovered a new process for the preparation of such isomers; the advantage of this process is that it facilitates the production of pure isomers. This is of particular importance in this case since the pharmacological activity of one isomer in standard tests for bronchodilator action is very much greater than that of the other.

The present invention therefore relates to a process for the preparation of optical enantiomers of α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^2 - diol (I):



(I)

and physiologically acceptable acid addition salts thereof, which comprises treating a basic ester of the general formula II:



(II)

in which AlK represents a straight or branched chain alkyl radical containing 1 to 6 carbon atoms with an optically active form of di - *p* - toluoyl tartaric acid in an organic solvent, crystallising the product, isolating a selected crystalline fraction, and recovering from said fraction an optical enantiomer of formula II, whereafter the optical enantiomer of formula I is recovered either as such or in the form of an acid addition salt by removal of the protective benzyl groups, with previous, simultaneous or subsequent conversion of the —COOAlk group to a group —CH_2OH.

The organic solvent in which the optically active form of di - *p* - toluoyl tartaric acid is dissolved is preferably an organic ester, such as ethyl acetate. The group —COOAlk may be converted to the group —CH_2OH by reduction with a suitable metal hydride or complex metal hydride, e.g. lithium aluminium hydride whilst the protective benzyl groups may be removed by catalytic hydrogenolysis over a noble metal catalyst e.g. a palladium charcoal catalyst.

The R(−) isomer of (I) has been found to be approximately fifty times more active than the S(+) isomer in antagonising the increased bronchial resistance produced by administration of acetyl chlorine in the anaesthetised guinea-pig (Konzett-Rossler preparation). The isomers (as the acetate-monomethanolate) have the following physical characteristics:

[Price 25p]

	m.p.	$[\alpha]_D^{23}$	c(MeOH)
R(−) isomer	143.9°C	+36.9°	0.23
S(+) isomer	143.0°C	−36.9°	0.27

The isomers themselves have the following characteristics:

R(−) isomer	−26°	0.36
S(+) isomer	+25°	0.4

In a further aspect of the invention therefore there are provided optically isomeric forms of the compound of formula I and their salts. The invention also provides pharmaceutical compositions comprising said isomers or their salts.

The invention also extends to the optically pure methyl esters of formula II.

Such pharmaceutical compositions may include as carrier any material conventionally referred to as such and includes excipients and formulatory agents. The compositions may contain supplementary medicinal agents if desired. Suitable solid carriers include maize starch, calcium sulphate dihydrate, lactose etc.

The compositions may include for instance solid and liquid preparations for oral use, suppositories, injections, or forms suitable for administration by inhalation.

Oral administration is most convenient in the form of tablets which may be prepared according to conventional methods, and may be coated if required. Soluble tablets suitable for sublingual administration may also be used.

Injections may be formulated with the aid of physiologically acceptable carriers and agents as solutions, suspensions or as dry products for reconstitution before use.

For administration by inhalation the compositions according to the invention are conveniently in the form of an aerosol spray presentation.

The following Examples illustrate the invention: (in these Examples as elsewhere in the Specification the abbreviation *t* in relation to butyl means tertiary).

Example 1

Resolution of *dl* - 5 - (2 - Benzyl - *t* - butylamino - 1 - hydoxyethyl) - 2 - benzyloxybenzoic acid, methyl ester and conversion into the (+) and (−) isomer of α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - α^1,α^3-diol

(−) - 5(2 - Benzyl - *t* - butylamino - 1 - hydroxyethyl) - 2 - benzyloxy benzoic acid, methyl ester.

A solution of the racemic base (30 g.) prepared by condensing methyl 2 - benzyloxy - 5 - bromoacetyl benzoate [see Collin et al, J. Med. Chem. *13* 674 (1970)] with *t* - butylbenzylamine in ethyl methyl ketone and reducing the crude product with sodium borohydride in ethanol by the general procedures already described in our United Kingdom Patent Specification No. 1,200,886 and (+) - O,O - di - *p* - toluoyltartaric acid (25.6 g.) in ethyl acetate (350 ml) at 70° was cooled slowly to room temperature and the precipitated salt was filtered off and dried (27 g., m.p. 130.0°, $[\alpha]_D^{23}$+49°, c=1, MeOH). Three recrystallisations from ethyl acetate gave material of constant rotation and melting point (m.p. 142.5° $[\alpha]_D^{23}$+47°, c=1.2, MeOH). This salt (10 g) in ethyl acetate was washed with sodium bicarbonate solution to remove the toluoyl tartaric acid.

The ethyl acetate was then evaporated and the residue recrystallised from petroleum ether (b.p. 40—60°C) to give the free base as colourless needles, (3 g, m.p. 87.0° $[\alpha]_D^{23}$−18.4, c=0.38, MeOH).

(+) - 5(2 - Benzyl - *t* - butylamino - 1 - hydroxyethyl) - 2 - benzyloxybenzoic acid, methyl ester.

This material was isolated from a procedure similar to the above using (−) - O,O - di - *p* - toluoyl tartaric acid as the resolving agent. Thus a solution of the racemic base (30 g) and (−) - O,O - di - *p* - toluoyl tartaric acid (25.6 g) in ethyl acetate (350 ml) deposited a salt, (27 g. m.p. 134—5° $[\alpha]_D^{23}$−48°, c=1, MeOH). Three recrystallisations from ethyl acetate gave material with constant m.p. 141.5° and $[\alpha]_D^{23}$−47°, c=1.5, MeOH. This salt (11 g) in ethyl acetate was converted into the *free base*, by extraction of the (−) - O,O - di - *p* - toluoyl tartaric acid with sodium bicarbonate solution. The ethyl acetate was removed and the residue recrystallised from petroleum ether (b.p. 40—60°) to give the free base (4.5 g., mp 87.0° $[\alpha]_D^{23}$+18.3, c=0.35, MeOH).

(+) - α^1 - *t* - Butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^3 - diol acetate

A solution of (−) - 5(2 - Benzyl - *t* - butylamino - 1 - hydroxyethyl) - 2 - benzyloxy benzoic acid, methyl ester (2.5 g) in dry tetrahydrofuran was added during 5 minutes to a stirred suspension of lithium aluminium hydride (0.5 g) in dry tetrahydrofuran (50 ml) and the mixture was heated to reflux and then allowed to cool. Excess hydride was decomposed with water and the product extracted with ether. Evaporation of the ether gave α^1 - benzyl - *t* - butylaminomethyl - 4 - benzyloxy - m - xylene - α^1,α^3 - diol (2.1 g) as a colourless oil that was hydrogenated (50 ml) in the presence of 10%

palladium on carbon (0.7 g) until uptake ceased. Removal of the catalyst and solvent gave (+) - α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^3 - diol as a colourless gum ($[\alpha]_D^{24}$ +25°, c=0.4, MeOH). This was converted into a crystalline acetate salt (m.p. 143.0°, $[\alpha]_D^{23}$ +36.9°, c=0.23, MeOH (from methanol:ether). Analysis of this salt confirmed the presence of one molecule of methanol of crystallisation.

(−) - α^1 - *t* - Butylaminomethyl - 4 - hydroxy - m - xylene - α^1,α^3 - diol acetate

In a manner similar to that above (+) - 5(2 - benzyl - *t* - butylamino - 1 - hydroxyethyl) - 2 - benzyloxybenzoic acid, methyl ester was reduced with lithium aluminium hydride and then hydrogenated to give (−) - α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^3 - diol ($[\alpha]_D^{24}$ −26°, c=0.36, MeOH). The acetate salt monomethanolate had mp 143.9°, $[\alpha]_D^{23}$ −36.9°, c=0.27, MeOH.

The following are Examples of pharmaceutical compositions containing isomers or their salts according to the invention. In each case the term active ingredient means one of the two isomers or their salts prepared according to Example I.

Example 2

Tablets suitable for oral administration.

Formula	1 mg Tablet	10,000 Tablets.
active ingredient	1.2 mg	12.0 g
calcium sulphate dihydrate	88.2 mg	882.0 g
maize starch	24.0 mg	240.0 g
Amijel	6.0 mg	60.0 g
magnesium stearate	0.6 mg	6.0 g
	120.0 mg	1200.0 g

Method

1. All the ingredients except the magnesium stearate, are mixed together, the mixed powders are graulated with water, and the damp mass is passed through a 16 mesh screen.

2. The wet granules are dried, and then passed through a 20 mesh screen.

3. The dried granules and the magnesium stearate are mixed together and compressed on a suitable tablet machine fitted with ¼" normal convave punches, to produce the required tablets.

Example 3

An aerosol formulation, expressed in terms of a single metered dose.

Formula	100 µg dose
active ingredient	100 µg
oleic acid	10 µg
dichlorodifluoromethane	61 mg
trichlorofluoromethane	24 mg

Method

The active ingredient, the oleic acid and part of the trichlorofluoromethane are mixed together. The suspension is then diluted with the remainder of the trichlorofluoromethane, and the requisite quantity is filled into aluminium aerosol containers which are closed by a suitable metering valve. The containers are then pressurised with dichlorodifluoromethane.

Example 4

Formula	100 µg dose
active ingredient	120 µg
sorbitan Trioleate	120 µg
Dichlorodifluoromethane B.P.C.	61 mg
Trichlorofluoromethane B.P.C.	24 mg

Method

Mix together the active ingredient, sorbitan trioleate, and part of the trichlorofluoromethane. The suspension is then diluted with the remainder of the trichlorofluoromethane and the requisite quantity of filled into aluminium aerosol containers, which are closed by a suitable metering valve. The containers are then pressurised with dichlorodifluoromethane.

Example 5

Formula	100 µg dose
active ingredient	120 µg
2-dimethylaminoethanol	26.6 µg
Oleic acid B. P. 1963	93.4 µg
Dichlorodifluoromethane B.P.C.	61 mg
Trichlorofluoromethane B.P.C.	24 mg

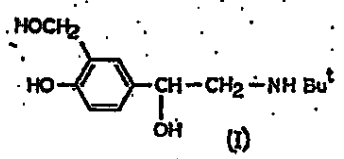
Method

The active ingredient, the oleic acid, 2 - dimethylaminoethanol and part of the trichlorofluoromethane are mixed together. The suspension is then diluted with the remainder of the trichlorofluoromethane, and the requisite quantity is filled into aluminium aerosol containers, which are closed by a

suitable metering valve. The containers are then pressurised with dichlorodifluoromethane.

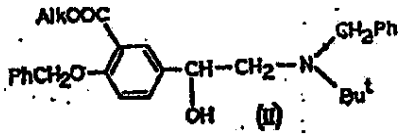
WHAT WE CLAIM IS:—

1. A process for the preparation of optical enantiomers of α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^3 - diol (I):



(I)

and physiologically acceptable acid addition salts thereof, which comprises treating a basic ester of the general formula II:



(II)

in which Alk represents a straight or branched chain alkyl radical containing 1 to 6 carbon atoms with an optically active form of di - *p* - toluoyl tartaric acid in an organic solvent, crystallising the product, isolating a selected crystalline fraction, and recovering from said fraction an optical enantiomer of formula II, whereafter the optical enantiomer of formula I is recovered either as such or in the form of an acid addition salt by removal of the protective benzyl groups, with previous, simultaneous or subsequent conversion of the —COOAlk group to a group —CH_2OH.

2. A process as claimed in claim 1 in which the organic solvent used for the resolving acid is an organic ester.

3. A process as claimed in claim 2 in which the solvent is ethyl acetate.

4. A process as claimed in any of claims 1 to 3 for the production of compounds of formula I in which prior to the removal of the protective groups, the COOAlk group is converted to a group —CH_2OH by reduction with lithium aluminium hydride, and in which the protective groups are then removed by catalytic hydrogenolysis with a palladium charcoal catalyst.

5. A process as claimed in claim 4 for the production of the (+) isomer of α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^3 - diol, which comprises preparing the salt of (+) - O,O - di - *p* - toluoyl tartaric acid and the *dl* racemate of 5(2 - benzyl - *t* - butylamino - 1 - hydroxyethyl) - 2 - benzyloxy benzoic acid, methyl ester in an organic solvent, recovering a selected salt of constant rotation by fractional crystallisation, decomposing said salt to recover (—) isomer of the ester, reducing said ester with lithium aluminium hydride and hydrogenating the product using a palladium charcoal catalyst.

6. A process as claimed in claim 4 for the production of the (—) isomer of α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene α^1,α^3 - diol, which comprises preparing the salt of (—) - O,O - di - *p* - toluoyl tartaric acid and the *dl* racemate of 5(2 - benzyl - *t* - butylamino - 1 - hydroxyethyl) - 2 - benzyloxy benzoic acid, methyl ester in an organic solvent, recovering a selected salt of constant rotation by fractional crystallisation, decomposing said salt to recover the (+) isomer of the ester, reducing said ester with lithium aluminium hydride and hydrogenating the product using a palladium charcoal catalyst.

7. A process as claimed in claim 1 substantially as herein described with reference to Example 1.

8. Optical enantiomers of α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^3 - diol and physiologically acceptable acid addition salts thereof when prepared by a process as claimed in any of claims 1 to 7.

9. The R(—) isomer of α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^3 - diol in the form of the acetate monomethanolate having m.p. 143.9°C and $[\alpha]_D^{25}$—36.9°, c (MeOH)=0.27.

10. The S(+) isomer of α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^3 - diol in the form of the acetate monomethanolate having m.p. 143.0°C and $[\alpha]_D^{25}$+36.9°, c (MeOH)=0.23.

11. The R(—) isomer of α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^3 - diol having $[\alpha]_D^{24}$—26°, c=0.36 MeOH.

12. The S(+) isomer of α^1 - *t* - butylaminomethyl - 4 - hydroxy - *m* - xylene - α^1,α^3 - diol having $[\alpha]_D^{24}$+25°, c=0.4 MeOH.

13. A pharmaceutical composition comprising as active ingredient or as one such ingredient an optical enantiomer as claimed in claim 8 in association with a non-toxic pharmaceutical carrier.

14. A composition as claimed in claim 13 adapted for oral use.

15. A composition as claimed in claim 13 adapted for parenteral administration.

16. A composition as claimed in claim 13 adapted for inhalation.

17. Compositions as claimed in any of claims 13 to 16 in which the active ingredient is or includes the acetate monomethanolate denfied in claim 9 or claim 10.

18. Compositions as claimed in any of

claims 13 to 16 in which the active ingredient is or includes the diol defined in claim 11 or 12.

19. Compositions as claimed in claim 13 substantially as herein described with reference to any one of Examples 2 to 5.

20. (—) - 5(2 - Benzyl - *t* - butylamino - 1 - hydroxyethyl) - 2 - benzyloxy benzoic acid, methyl ester, m.p. 87.0°C, $[\alpha]_D^{25}$ — 18.4, c=0.28, MeOH.

21. (+) - 5(2 - Benzyl - *t* - butylamino - 1 - hydroxyethyl) - 2 - benzyloxy benzoic acid, methyl ester m.p. 87.0°C, $[\alpha]_D^{25}$ + 18.3, c=0.35 MeOH.

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(56) Documents cited
EP 0455155 A1 WO 91/09596 A1
Chem. Pharm. Bull. 26(4), 1123-9 (1976)
J. Med. Chem. 14(9), 895-6 (1971)
J. Liq. Chromatogr. 11, 2147-63 (1988)
Biochem. Pharmacol. 35(12) 1981-5, (1986)
Br. J. Clin. Pharmacol. 27, 49-56, (1989)

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(54) Bronchodilator enantiomers

(57) Improved use of selective β_2 sympathomimetic bronchodilator drugs in the therapy of obstructive or inflammatory airways disease, e.g. asthma, comprises use in enantiomeric rather than conventional racemic form. The improved use reduces occurrence of side effect; e.g. exacerbation of basal disease status or compromise or deterioration of lung function. The active compound is used in the form of its R-enantiomer e.g. Albuterol, Terbutaline, Fenoterol, Metaproterenol, Orciprenaline, Carbuterol or Isoetharine, optionally in combination with Ketotifen.

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IMPROVED USE OF β_2 BRONCHODILATOR DRUGS

The present invention relates to a new and improved use of selective β_2 sympathomimetic bronchodilator drugs in the therapy of obstructive or inflammatory airways disease, especially asthma.

Bronchodilator drugs employed in the therapy of obstructive or inflammatory airways disease, e.g. asthma, are divisible into three classes:

1. Adrenergic or sympathomimetic drugs (the terms "adrenergic" and "sympathomimetic" are used in the art interchangeably);
2. Anticholinergic drugs; and
3. Methylxanthine drugs.

The present invention is concerned with the first of these drug classes.

The adrenergic or sympathomimetic drugs are so called because they are understood to exert their effect through their action on the body's adrenergic receptors of which there are three functionally divided types, the α, β_1 and β_2 receptors. On the basis of their interaction with these three receptor types, the adrenergic or sympathomimetic drugs are in turn classifiable into three groups:

1.1 Non-selective sympathomimetic drugs;
1.2 Non-selective β sympathomimetic drugs; and
1.3 Selective β_2 sympathomimetic bronchodilator drugs.

drugs of group 1.1 exert both α and β sympathomimetic effects. They include the drug substances adrenaline and ephedrine. Both adrenaline and ephedrine are known clinically as bronchodilators. Though adrenaline, despite side effect induced via its α-sympathomimetic properties, is still used by some practitioners for the treatment of acute asthma, both adrenaline and ephedrine have been largely superseded in asthma therapy.

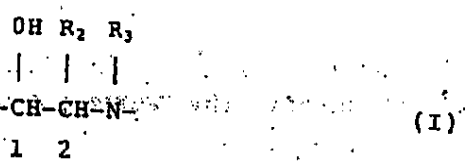
The drugs of group 1.2 have both β_1 and β_2 sympathomimetic activity but no, or only limited, α-sympathomimetic activity. Of the group 1.2 drugs, isoprenaline is the best known representative. Isoprenaline differs from the drugs of group 1.3 in its faster onset but shorter duration of action and its cardiac stimulating effects which result largely from its β_1 activity. Though isoprenaline has previously been extensively used as bronchodilator therapy in asthma, its use has today become clinically restricted. Thus, in the UK, a rise in the rate of asthma death in the 1960's believed to have been specifically associated with isoprenaline usage has resulted in discontinuation of its clinical application.

The selective β_2 sympathomimetic bronchodilator drugs of group 1.3 (herein referred to for convenience collectively as "GROUP 1.3 DRUGS") act, as their name implies, selectively on the β_2 adrenergic receptors. The GROUP 1.3 DRUGS include for example, the drug substances a) TERBUTALINE, b) ALBUTEROL (also known as SALBUTAMOL), c) FENOTEROL, d) HEXOPRENALINE, e) RIMITEROL, f) ISOETHARINE, g) METAPROTERENOL, h) REPROTEROL, i) CLENBUTEROL, j) PROCATEROL, k) CARBUTEROL, l) TULOBUTEROL, m) PIRBUTEROL, n) BITOLTEROL and, more recently, the so-called "long acting selective β_2 sympathomimetic bronchodilator drug substances" o) FORMOTEROL, p) BAMBUTEROL and q) SALMETEROL [(R,S)-1-(4-hydroxy-3-hydroxymethylphenyl)-2-[6-(4-

phenylbutoxy)hexylamino]ethanol]. All of the above recited GROUP 1.3 DRUGS are commercially available and clinically used, generally in pharmaceutically acceptable salt form, e.g. as the sulphate [(a), (b), (d) and (g)], hydrobromide [(c) and (e)], hydrochloride [(f), (h) to (l) and (p)], dihydrochloride [(d) and (m)], fumarate [(o)], methanesulfonate [(n)], hydroxynaphthoate [(q)] or, where appropriate, one or other of the hydrate forms thereof - see e.g. Merck Index, 11th edition (1989), items 9089 (a), 209 (b), 3927 (c), 4628 (d), 8223 (e), 5053 (f), 5836 (g), 8142 (h), 2347 (i), 7765 (j), 1840 (k), 9720 (l), 7461 (m), 1317 (n), 4159 (o) and 963 (p) and references cited therein and, for (q), Am. Rev. Resp. Dis. 137 (4; 2/2) 32 (1988).

Further GROUP 1.3 DRUGS currently in development include for example the drug substances r) BROXATEROL, s) ETANTEROL, t) MOXITEROL, u) NAMINTEROL, v) PICUMETEROL, w) RP 58802 [Rhône-Poulenc], x) RU 42173 [Hoechst Roussel-Uclaf] and y) ZK 90055 [Schering].

GROUP 1.3 DRUGS characteristically contain as part of their structure an ethanolamine or 2-amino-ethanol moiety of formula I



(I)

in which R_1 is an aromatic group.

Commonly R_1 is 3,4- or 3,5-dihydroxyphenyl as in the case of the GROUP 1.3 DRUGS (a), (c), (d), (e), (f), (g) and (h) above or 4-hydroxy-3-hydroxymethylphenyl as in the case of the GROUP 1.3 DRUGS (b) and (q). R_1 may also be, e.g., 2-hydroxymethyl-3-hydroxy-6-pyridyl; 3,4-ditoluoyloxyphenyl; 3-formylamino-4-hydroxyphenyl;

3,5-N,N-dimethylcarbamoyloxyphenyl; 4-amino-3,5-dichlorophenyl; 4-hydroxy-3-ureidophenyl; or 2-chlorophenyl as in the case of the GROUP 1.3 DRUGS (l), (m), (o), (p), (i), (k) and (l) respectively.

R_3 in formula I is commonly H. An exception in this respect is the GROUP 1.3 DRUG (e) above. In this case R_2 and R_3 together are a group of formula $-(CH_2)_4-$.

R_2 in formula I is also commonly H. Exceptions in this respect are the GROUP 1.3 DRUG (e), as noted above, as well as (f) and (j) in both of which R_2 is ethyl.

Since the formula I moiety comprises at least 1 asymmetric carbon atom (C1 in formula I), all of the GROUP 1.3 DRUGS exist in optically active isomeric form, with the said carbon atom having the (R) or (S) configuration [as designated using the Cahn-Ingold-Prelog system (Angew. Chem. Intern. Ed. 5, 385-415 (1966)]. When the said carbon atom is the sole asymmetric carbon atom present, GROUP 1.3 DRUGS thus exist as individual (R) or (S) enantiomers or in racemic [(RS)] form, i.e. as a 50:50 mixture of the (R) and (S) enantiomers.

Individual GROUP 1.3 DRUGS in which R_2 in the formula I moiety is other than H or in which the remainder of the molecule includes an asymmetric carbon atom exist in a variety of isomeric forms, i.e. in individual (R,R), (S,S), (R,S) and (S,R) isomeric form, as racemic [(RS,RS) and (RS,SR)] mixtures comprising the (R,R) plus (S,S) and (R,S) plus (S,R) enantiomeric pairs, as well as in the form of diastereomeric mixtures comprising all four isomeric forms. This is so, for example, in the case of the GROUP 1.3 DRUGS (c), (d), (e), (f) and (o) above.

Individual enantiomers [e.g. (R) or (S), or (R,R) or (S,S) enantiomers] of GROUP 1.3 DRUGS are known and have been

described together with processes for their production in the literature. Pharmacological studies and clinical, e.g. metabolic, investigations employing healthy volunteers have also been carried out using individual enantiomers of GROUP 1.3 DRUGS. It is furthermore known that the β_2-sympathomimetic/bronchodilator activity of GROUP 1.3 DRUGS resides primarily in individual enantiomers in which the hydroxy bearing carbon atom, C1 in formula I has the (R) configuration. The corresponding (S) enantiomer in contrast has no or very little bronchodilator activity. [See e.g. Murase et al., Chem. Pharm. Bull., 26 (4), 1123-1129 (1976); Hartley et al., J. Med. Chem. 14 (9), 895-896 (1971); Okamoto et al., J. Liq. Chromatogr. 11, 2147-2163 (1988), Koster et al., Biochem. Pharmacol., 35 (12), 1981-1985 (1986), Borgström et al., Br. J. Clin. Pharmac., 27, 49-56 (1989) and references therein.]

This knowledge notwithstanding, GROUP 1.3 DRUGS are marketed and employed for regular clinical usage, e.g. in the treatment of obstructive or inflammatory airways disease, in racemic [(RS)] form, that is as mixtures of the bronchodilatatorily active (R) and inactive (S) enantiomeric pairs. [In the case of GROUP 1.3 DRUGS comprising two asymmetric carbon atoms the clinically employed racemic mixture is commonly that comprising the (R,R) plus (S,S) enantiomeric pair, i.e. the (RS,RS) racemate, as in the case of the so called "A racemate" of FENOTEROL - cf. Merck Index, Loc. cit.]

The GROUP 1.3 DRUGS can be administered orally, parenterally or (most commonly) by inhalation, e.g. using nebulisers or metered aerosol devices or as inhaled powders. Inhalation of GROUP 1.3 DRUGS presently represents the mainstay of bronchodilator therapy for the treatment of asthma of all grades of severity. The duration of bronchodilatation induced by the majority of GROUP 1.3 DRUGS is relatively short and they are employed to relieve asthma attack as and

when it occurs. As indicated above, the more recently introduced GROUP 1.3 DRUGS, e.g. (o), (p) and (q) above, are characterised by their longer duration of action and hence apparent reduced frequency of dosaging required.

Although the GROUP 1.3 DRUGS are effective and generally seem to be well tolerated, their safety, especially at high dosages, has been questioned over many years and numerous reports have appeared on the adverse effects of GROUP 1.3 DRUG therapy (see e.g. Paterson et al: "American Review of Respiratory Disease, 120, 844 to 1187 (1979) especially at p.p. 1165 et seq.). More recently, from New Zealand, where a continuing increase in asthma death has been recorded, two case control studies reported in the Lancet have linked increase in asthma mortality to use of the GROUP 1.3 DRUG, FENOTEROL - see in particular: Editorial "β_2 agonists in asthma: relief, prevention, morbidity", Lancet, 336, 1411-1412 (1990). A subsequently reported Canadian study finds that the use of inhaled GROUP 1.3 DRUGS, principally FENOTEROL and ALBUTEROL, is associated with "an increased risk of the combined outcome of fatal and near-fatal asthma, as well as of death from asthma alone" - see Spitzer et al., New England J. of Med., 326 (8), 501-506 (1992) and the Editorial to the same issue at page 560.

Various possible explanations for observed episodes of increased airway obstruction, arterial hypoxaemia or "anomolous" or "paradoxical" bronchospasm, as well as increased morbidity associated with GROUP 1.3 DRUG usage, in particular long term/high dose usage, have been proposed.

These have included, for example, reactive myogenic tone, increased inflammatory burden, adrenoceptor tachyphylaxis and induction of airway hyperreactivity, as well as the involvement of spasmogenic drug metabolic products or long term influence of aerosol spray propellants - see e.g. Paterson et al. loc. cit. and Morley et al. Eur. Respir. J.,

1-5 (1990).

already noted, an increase in asthma death had earlier
en associated with use of the GROUP 1.2 DRUG isoprenaline.
oprenaline is metabolised in part by the enzyme
techol-O-methyl transferase, giving a 3-methoxy derivative
ich has β-adrenoceptor antagonist activity. It has, for
ample, been suggested that it is this metabolite which was
e cause of difficulty. More recently it has been proposed
at isoprenaline-induced asthmatic exacerbation is due to
exacerbation of airways-hyperreactivity or inflammatory
atus common to the (S) [or (+)] and (R) [or (-)]
antiomers of isoprenaline [see e.g. : Mazzoni et al.,
it. J. Pharmacol, 91, 326 (1987); Morley et al., J.
ysiol, 390, 180 P (1987) and Lancet, July 16, 1988, p.
0; and Sanjar et al., J. Physiol, 425, 43-54 (1990) -
oprenaline like the GROUP 1.3 DRUGS was employed
inically in (RS) racemic [or (±)] form.] No consensus on
e subject has however been reached within the scientific
mmunity and no evidence has hitherto been adduced which
ght link experience with isoprenaline to that with GROUP
3 DRUGS.

the same time there is mounting concern within the
dical profession as to the potential dangers of GROUP 1.3
UG usage in asthma therapy. To quote the Lancet Editorial
ready referred to:
hese studies raise serious question about the use of β_2
onists [i.e. GROUP 1.3 DRUGS]. The findings of Sears et
. could be interpreted as supporting the current trend
wards earlier use of corticosteroids and other preventers
inflammation [for asthma therapy] rather than
erseverence with an escalating bronchodilator regimen. The
ndings of the Nottingham and Dunedin groups also indicate
at there is some way to go before long acting β_2 agonist
eparations such as salmeterol and formoterol can be
reservedly recommended for routine use in the management

of asthma. There seem to be clear advantages of compliance and possibly of anti-inflammatory activity associated with such agents, but the potential for adverse effects cannot be ignored. Clinicians researchers and pharmaceutical companies must now attempt to redefine the use of β_2 agonists in asthma." [Emphasis added.]

Equally there has been evident inability or reluctance to conceive of any problem in relation to GROUP 1.3 DRUG therapy as being inherent in GROUP 1.3 DRUGS themselves or as hitherto employed - cf. the following, taken from the Editorial to the New England Journal of Medicine also previously referred to: "Although ... too much reliance is placed on beta-agonists [GROUP 1.3 DRUGS], it is difficult to believe that the problem is related directly to the more regular use of inhaled beta-agonists."

In accordance with the present invention it has now been found that, whereas bronchodilator efficacy of GROUP 1.3 DRUGS is associated with, or associated primarily with, one optically active enantiomer, the bronchodilatatory less active or inactive enantiomer or antipode induces an adverse effect, e.g. in asthma. (This finding does not, of course, exclude the possibility that the isomer having bronchodilator efficacy may also possess adverse pharmacological properties which are masked or compensated for by its beneficial bronchodilator efficacy.) The present invention thus surprisingly teaches that the long-standing problems inherent in GROUP 1.3 DRUG therapy may unexpectedly be met or ameliorated by the relatively simple expedient of administering GROUP 1.3 DRUGS not, as hitherto, in the form of a racemic mixture but in the form of the individual bronchodilatatory effective enantiomer (referred to hereinafter for convenience as the "BRONCHODILATOR ENANTIOMER").

While the suitability, in particular of high-dose or

long-term, GROUP 1.3 DRUG therapy has long been a subject of debate and, more recently, acute question, the practice of administering drugs of this group as racemic mixtures has continued. This practice has been accepted by drug registration authorities world-wide and even the most recently introduced of the GROUP 1.3 DRUGS have been developed for clinical use as racemic mixtures.

This practice is based upon the assumption or understanding that the non-bronchodilator component of the racemic mixture, i.e. the bronchodilatorily less or inactive enantiomer or antipode of the BRONCHODILATOR ENANTIOMER is devoid of any relevant drug effect and can thus be administered together with the BRONCHODILATOR ENANTIOMER essentially as inactive ballast and without risk to the patient. The teaching of the invention thus stands in stark opposition to long, widely established and continuing practice.

While simple in conception, the present invention thus runs contrary to to the wisdom of the art. In that the GROUP 1.3 DRUGS clearly offer very considerable potential benefit for bronchodilator usage in asthma, the need to find a means of avoiding, ameliorating or restricting disadvantages inherent in their use is urgent and crucial. By meeting this need, the present invention may be anticipated to bring immeasurable benefit both to the medical profession and the world asthma population.

In accordance with the foregoing the present invention provides:

A An improved (e.g. safer) method of treating inflammatory or obstructive airways disease or a method of treating inflammatory or obstructive airways disease with the avoidance, amelioration or restriction of deleterious side effect, in a human subject in need thereof, which

method comprises administering to said subject a GROUP 1.3 DRUG, said GROUP 1.3 DRUG being administered predominantly in the form of its BRONCHODILATOR ENANTIOMER; or, in the alternative:

B A GROUP 1.3 DRUG predominantly in the form of its BRONCHODILATOR ENANTIOMER for use in the improved (e.g. safer) treatment of inflammatory or obstructive airways disease in humans, or for use in the treatment of inflammatory or obstructive airways disease in humans to avoid, ameliorate or restrict deleterious side effect, or for use in the preparation of a pharmaceutical composition for use in such treatment.

GROUP 1.3 DRUGS to which the present invention applies include any selective β_2 sympathomimetic bronchodilator drug comprising an ethanolamine moiety, e.g. of formula I as illustrated above wherein R_1 is an aromatic group, for example a moiety of formula I as illustrated above wherein R_1, R_2 and R_3, individually or collectively have any one or more of the meanings hereinbefore recited.

Specific GROUP 1.3 DRUGS to which the present invention applies include any of the drug products (a) through (y), especially (a) through (q) hereinbefore identified and, in particular, (b) ALBUTEROL and the "long acting" GROUP 1.3 DRUGS, in particular (o) FORMOTEROL, (p) BAMBUTEROL and (q) SALMETEROL. The invention is to be understood as relating to GROUP 1.3 DRUGS both in free form as well as pharmaceutically acceptable acid addition salt form, e.g. as hereinbefore set forth for the GROUP 1.3 DRUGS (a) through (q), and including hydrate forms thereof. All references to GROUP 1.3 DRUGS, whether individually or collectively and in whatever manner, in relation to the present invention both herein and in the accompanying claims are to be understood accordingly as embracing such salt and hydrate forms.

As hereinbefore described in relation to formula I, C1 in BRONCHODILATOR ENANTIOMER of GROUP 1.3 DRUGS characteristically has the (R) configuration. In the case of GROUP 1.3 DRUGS having a single asymmetric carbon atom BRONCHODILATOR ENANTIOMER will thus be the (R) enantiomer. In the case of GROUP 1.3 DRUGS having two asymmetric carbon atoms BRONCHODILATOR ENANTIOMER will be the (R,R) or (R,S) isomer. In practice, GROUP 1.3 DRUGS having two asymmetric carbon atoms have hitherto been used in clinic generally in the form of the (RS,RS) racemic mixture and it is the (R,R) enantiomer which generally has the greatest bronchodilator potency (see e.g. Murase et al., loc. cit.). In the case of GROUP 1.3 DRUGS hving two asymmetric carbon atoms BRONCHODILATOR ENANTIOMER will thus usually be the (R,R) enantiomer.

In practicing the present invention, GROUP 1.3 DRUG is employed predominantly in the form of its BRONCHODILATOR ENANTIOMER. Preferably GROUP 1.3 DRUG will be employed in the form of its pure or substantially pure BRONCHODILATOR ENANTIOMER, that is in a form free or substantially free of other isomeric forms, in particular of the chirally opposite ("non-bronchodilator") antipode. Suitably GROUP 1.3 DRUGS will comprise at least >75%, preferably at least 90%, e.g. >95% or >98% BRONCHODILATOR ENANTIOMER. As previously indicated GROUP 1.3 DRUGS in pure or substantially pure isomeric form are known [see for example Murase et al. and Hartley et al. loc. cit. and other references referred to in the Merck Index hereinbefore cited] or may be obtained analogously, e.g. by resolution of diastereomeric salt forms/chromatographic techniques.

The present invention provides a method or use for the treatment of inflammatory airways disease, in particular for effecting bronchodilatation, e.g. as a means of alleviating airways obstruction, in particular acute airways obstruction, e.g. asthma attack, occurring in such disease.

the invention thus provides symptomatic, rather than prophylactic, therapy for such disease.

The teaching of the present invention is applicable in the therapy of inflammatory or obstructive airways disease, in particular any such disease for which GROUP 1.3 DRUG therapy is commonly practiced, for example chronic obstructive pulmonary disease, e.g. consequential to cystic fibrosis, emphysema and, especially, chronic bronchitis and, most especially, asthma.

The present invention avoids deleterious side effects hereinbefore resulting or observed in, e.g. asthmatic, patients consequent to conventional clinical usage of GROUP 1.3 DRUGS as racemic mixtures. In particular the invention provides means to avoid, ameliorate or restrict deleterious side effect, e.g. side effect deleterious to the airways. Thus the invention provides means to avoid, ameliorate or restrict exacerbation of disease status, for example basal disease, e.g. basal asthmatic, status or to avoid, ameliorate or restrict compromise or deterioration of lung function, or any other side effect concomitant to conventional clinical usage, for example "anomolous", "rebound" or "paradoxical" bronchospasm and, especially, increase in airway obstruction, exacerbation of late asthmatic response or non-specific bronchial reactivity or arterial hypoxaemia. Without limiting the present invention to any specific theory or mode of action, the present invention is in particular to be understood as providing a means for the avoidance, amelioration or restriction of exacerbation of airways hyperreactivity and/or of inflammatory or other event associated with, or which is an aetiological component of, inflammatory or obstructive airways disease, e.g. asthma. Such events are to be understood as including for example, inflammatory cell infiltration of the lungs or airways, connective tissue deposition or smooth muscle hyperplasia within the lungs or

airways or other morphological change associated with asthmatic status. The present invention also provides a means of preventing or reducing morbidity, e.g. asthma morbidity, ascribable to conventional, e.g. high dosage or long term, GROUP 1.3 DRUG usage.

The present invention is especially applicable in the therapy of bronchial asthma of whatever type or genesis. It is applicable to both intrinsic and extrinsic asthma. It is especially applicable to the treatment of allergic or atopic (i.e. IgE-mediated) asthma or non-atopic asthma, as well as exercise induced asthma, occupational asthma, asthma induced following bacterial infection or drug, e.g. aspirin, ingestion and other non-allergic asthmas. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting chronic cough or wheezing symptoms, in particular at night, and diagnosed or diagnosable as "wheezy infants", i.e. as embracing the treatment of "wheezy infant syndrome". Other diseases to which the present invention is in particular applicable include for example chronic obstructive pulmonary or airways disease (COPD or COAD).

As previously mentioned, the present invention embraces the understanding that BRONCHODILATOR ENANTIOMERS of GROUP 1.3 DRUGS may themselves exhibit adverse pharmacological properties in common with the non-bronchodilator antipodes, which are masked, or compensated for, by their bronchodilator efficacy. As a direct corollary to this and in the light of the understanding of said adverse effects as taught by the invention, the therapeutic benefit of BRONCHODILATOR ENANTIOMERS may be yet further improved by co-administration of drug substances capable of reversing or inhibiting the development of airways hyperreactivity, notably the drug substance KETOTIFEN (cf. Merck Index, loc. cit. item 5187). Accordingly in a further aspect the present invention provides:

C A method as defined under A above, which method additionally comprises administration of KETOTIFEN; or

D A GROUP 1.3 DRUG predominantly in the form of its BRONCHODILATOR ENANTIOMER for use as defined under B above, wherein said use comprises use in conjunction with use of KETOTIFEN, i.e. additionally comprises administration of KETOTIFEN.

KETOTIFEN is known and commercially available, e.g. in pharmaceutically acceptable acid addition salt form, for example as its hydrogen fumarate, for use, inter alia, as an asthma prophylactic drug. References to KETOTIFEN herein are to be understood as embracing KETOTIFEN in free base form or in the form of any of its pharmaceutically acceptable acid addition salts.

For the above purposes KETOTIFEN will generally be administered in anti-asthmatically effective amount, i.e. at dosages conventionally administered for the prophylaxis of asthma, as hereinafter described. In practicing the invention KETOTIFEN may be administered either concomitantly with or independently of BRONCHODILATOR ENANTIOMER of GROUP 1.3 DRUG, e.g. in a separate daily regimen during the course of therapy employing BRONCHODILATOR ENANTIOMER of GROUP 1.3 DRUG.

The deleterious effects of the non-bronhcodilator enantiomer (i.e. antipode of BRONCHODILATOR ENANTIOMER) of GROUP 1.3 DRUGS, e.g. of (S)-ALBUTEROL and (S)-TERBUTALINE [the dextro or (+) optically active isomers] as well as the advantages obtaining from the application of the present invention may be demonstrated in conventional animal models as well as in clinical trials for example as follows:

Example 1: Influence of non-bronchodilator enantiomers of GROUP 1.3 DRUGS on airways hyperreactivity in the guinea pig

Guinea-pigs (circa 500g) are anaesthetised by intraperitoneal injection of sodium phenobarbitone (100mg/kg) and sodium pentobarbitone (30mg/kg) then paralysed by intramuscular injection of gallamine (10mg/kg). Animals are ventilated (8ml/kg, 1Hz) via a tracheal cannula using a mixture of air and oxygen (50:50, v/v). Ventilation is monitored at the trachea by a pneumotachograph (type 0000, Fleisch, Zabona A.G., CH) connected to a differential pressure transducer (type MP 4514871, Validyne, USA). Coincident pressure changes within the thorax are measured via an intrathoracic cannula, using a differential pressure transducer (type MP 4524, Validyne, USA); blood pressure and heart rate are recorded from the carotid artery using a pressure transducer (type P23Dd, Gould, USA). From measurements of air-flow and intrathoracic pressure, both airway resistance (R_L) and compliance (C_{dyn}) are calculated at each respiratory cycle using a digital electronic pulmonary monitoring system (PMS, Mumed Ltd, London, UK) and recorded. Blood pressure, intrathoracic pressure, airflow and computed R_L and C_{dyn} in real time are displayed on a visual display unit (model AT3, IBM, USA). Experimental data is stored electronically and experimental traces or processed data are plotted on a laser printer (Laser Jet Series II, Hewlett Packard, USA) as required.

1) In a first series of experiments responsivity of the airways to intravenous injection of histamine (0.56-1.8µg/kg at 10 min. intervals) is defined before, and twenty minutes after, intravenous infusion of (S)-ALBUTEROL over one hour (total dose 100µg/kg). Increase of airway resistance following intravenous injection of histamine (0.56, 1.0 & 1.8µg/kg) in one experimental run is recorded as (10 ± 1.8, 41.03 ± 9.14 & 223 ± 69.91 $cmH_2O/l/sec.$) before and (60.01 ± 12.86, 149.06 ± 31.64

& 539 ± 185.14 $cmH_2O/l/sec.$) after infusion of (S)-ALBUTEROL (100μg/kg). Incremental differences for successive doses of histamine recorded are 50.1, 108.03 & 316 $cmH_2O/l/sec.$ By comparison, increased airway resistance in response to intravenous injection of histamine (0.56, 1.0 & 1.8μg/kg) before and after intravenous infusion of vehicle (0.9% saline) is recorded as (7.05 ± 1.17, 21.68 ± 3.05, 86.45 ± 14.13 and 15.04 ± 2.57, 30.42 ± 5.39, 101 ± 20 respectively) so that incremental differences for successive doses of histamine are 7.99, 8.74 & 14.75 $cmH_2O/l/sec.$

2) In a second series of experiments employing guinea pigs actively sensitised to ovalbumin [as described in Sanjar et al., Br. J. Pharmacol. 99, 679-686 (1990)], responsivity of the airways to intravenous injection of histamine (as under 1 above) before and after intratracheal instillation of tragant (0.2ml) alone or containing (S)-ALBUTEROL (10μg) or (S)-TERBUTALINE (10μg) is defined. In this test model both (S)-ALBUTEROL and (S)-TERBUTALINE are found to induce significant increase of airway resistance on intravenous injection of histamine as compared with animals receiving tragant only.

Similar or equivalent results are obtained employing non-bronchodilator enantiomer of other GROUP 1.3 DRUGS, e.g. the (S) or (S,S) enantiomer of GROUP 1.3 DRUGS (c) to (q) as hereinbefore set forth, at the same or equivalent dosage rates.

Example 2: Influence of non-bronchodilator enantiomer of GROUP 1.3 DRUGS on the lung function of asthmatic patients

The trial is carried out in double blind, placebo controlled format. Subjects are stable asthmatics with evident on-going

compromisation of lung function. Typical subjects include allergic asthmatics or non-allergic (intrinsic asthmatics) with no evidence of atopy, clinically stable and using conventional nebulised GROUP 1.3 DRUGS therapy regularly. Asthma medication is withdrawn ca. 12 hours prior to investigation and pulmonary function (FEV_1) is monitored at regular intervals prior to and following adminsitration of test substance or placebo (vehicle). Additionally PD20 for histamine is determined by measuring the effect of inhaled aerosols of histamine solutions (0.0625-8mg/ml) 0.5 hrs before as well as 2.5 and 7.5 hrs after exposure to test substance/vehicle.

Test substance comprises GROUP 1.3 DRUG administered by the inhaled route either in racemic form (in accordance with conventional practice) at conventional single dose level or in substantially pure non-bronchodilator enantiomeric form at 0.25 to 0.5 x the conventional single dose level.

In subjects receiving GROUP 1.3 DRUG in conventional, racemic form, e.g. receiving (R,S)-ALBUTEROL, (R,S)-TERBUTALINE or (RS,RS)-FENOTEROL, dose related reduction of airflow obstruction is observed as compared with subjects receiving placebo. Results thus accord with conventional observations for GROUP 1.3 DRUG therapy.

In subjects receiving GROUP 1.3 DRUG in substantially pure non-bronchodilator enantiomeric form, e.g. receiving (S)-ALBUTEROL, (S)-TERBUTALINE or (S,S)-FENOTEROL, after potential transient reduction in airflow obstruction attributable to any BRONCHODILATOR ENANTIOMER present in the administered material, individual subjects exhibit a sustained fall in FEV_1, accompanied by increased wheezing and discomfort as compared with results obtained from subjects receiving placebo.

In practicing the present invention, BRONCHODILATOR

ENANTIOMER of GROUP 1.3 DRUG may be administered in any form or by any route known or conventionally employed in relation to use of selected GROUP 1.3 DRUG in conventional racemic form, e.g. orally in the form of tablets, capsules, syrups, granulates and micro-granulates etc., intravenously in the form of an injectable solution, or by the pulmonary route. Preferably BRONCHODILATOR ENANTIOMER of GROUP 1.3 DRUG will be administered via the pulmonary route, e.g. by inhalation from an appropriate dispenser device, e.g. as hereinbefore indicated or as otherwise known or used in the art.

Dosages of BRONCHODILATOR ENANTIOMER of GROUP 1.3 DRUG employed in practicing the present invention will vary, e.g. depending on the particular GROUP 1.3 DRUG selected, the selected route of administration, the particular condition to be treated, the severity of the condition to be treated and the effect desired. In general however dosages of BRONCHODILATOR ENANTIOMER of the selected GROUP 1.3 DRUG will be of the order of about 40% to 60%, e.g. about 50%, of dosages administered employing the same GROUP 1.3 DRUG in conventional, racemic form. This lowering of the dosage may readily be achieved, e.g. by preparing galenic forms comprising BRONCHODILATOR ENANTIOMER of the selected GROUP 1.3 DRUG as active ingredient in the same concentration as in conventionally employed dosage forms and reducing the daily dosaging requirement by ca. 50%, or by preparing galenic forms comprising BRONCHODILATOR ENANTIOMER as active ingredient at ca. 50% of the concentration conventionally employed for GROUP 1.3 DRUG and maintaining conventional daily dosaging requirements. In the latter case, the 50% reduction in active ingredient content will be compensated by the addition of the equivalent amount of an appropriate, inert pharmaceutically acceptable diluent or carrier.

Thus for administration by inhalation, (R,S)-ALBUTEROL is conventionally administered, e.g. via a metered dose aerosol delivering 100μg racemic drug substance per actuation. For

adults, administration is conventionally effected 3 to 4 times/day with 2 actuations at each administration, to give a dosage per administration of 200μg drug substance. The canisters employed in the delivery device contain ca. 20mg (R,S)-ALBUTEROL or sufficient for 200 actuations.

Employing pure or substantially pure (R)-ALBUTEROL in accordance with the present invention, administration can be effected employing an identical regimen to that used for the racemate but using canisters containing ca. 10mg (R)-ALBUTEROL, giving a metered dose of 50μg drug substance per actuation or a dosage of 100μg drug substance 3 to 4 times/day, or using canisters containing ca. 20mg (R)-ALBUTEROL, giving a metered dose of 100μg drug substance per actuation and applying only 1 instead of 2 actuations at each administration.

From the foregoing it will be appreciated that suitable galenic formulations for practicing the present invention may be in all material respects identical to those employed for delivery of conventional, racemic GROUP 1.3 DRUG, but with appropriate compensation for reduction in active ingredient content where required.

As previously indicated, in practicing the present invention, BRONCHODILATOR ENANTIOMER of GROUP 1.3 DRUG is preferably administered by the pulmonary route, e.g. by inhalation. Compositions employed will thus preferably be in a form permitting, enabling or adapted for administration via the pulmonary route. Such forms will in particular include free flowing, or freely flowable, dispersible forms, for example liquid or finely divided powder forms, capable of or adapted to delivery as an inhalable spray, mist or dispersion in air, e.g. following delivery from an appropriate, e.g. aerosol, atomiser, dry powder dispenser or like device. Carriers, excipients, diluents etc. employed in such compositions will likewise preferably be selected from

amongst those known, employed and/or recognised as suitable for pulmonary administration.

The following examples are illustrative of compositions suitable for use in accordance with the present invention:

Example 3

3.1 Tablets or capsules may contain the active agent in admixture with conventional pharmaceutically acceptable excipients, e.g. inert diluents such as calcium carbonate, sodium carbonate, lactose and talc, granulating and disintegrating agents, e.g. starch and alginic acid, flavouring, colouring and sweetening agents, binding agents, e.g. starch, gelatin and acacia, and lubricating agents, e.g. magnesium stearate, stearic acid and talc, e.g. as follows:

INGREDIENTS	WT./DOSE
(R)-METAPROTERENOL (as its sulfate) in substantially pure form	20.00 mg
Lactose (200 mesh)	90.00 mg
Corn starch	35.00 mg
Silicon dioxide (Aerosil 200)	1.75 mg
Magnesium stearate	3.25 mg
TOTAL	150.00 mg

The ingredients are intimately admixed employing conventional galenic procedures, filled into hard gelatin capsules and the capsules sealed.

The capsules are useful in accordance with the present invention in the therapy of asthma on administration in adults 2x daily to give a daily dose of 40mg/day/p.o.. Alternatively capsules may be prepared comprising 10.00mg

R)-ORCIPRENALINE (as its sulfate) for administration in dults 4x daily.

quivalent oral compositions may be prepared comprising RONCHODILATOR ENANTIOMER of any other GROUP 1.3 DRUG, e.g. s hereinbefore referred to, either at conventional unit osage drug concentration* for administration at 50% onventional dosaging rate* or at 50% conventional unit osage drug concentration for administration at conventional osaging rate.

*For the drug substances TERBUTALINE, FENOTEROL and ARBUTEROL for example, conventional oral unit dosage forms comprising racemic material) comprise 2.5 or 5.0mg; 5.0 or 0.0mg; and 2.3mg racemic material respectively, for dministration 2 to 4x daily.]

2 Inhalable aqueous solutions may also be prepared in onventional manner, e.g. optionally with the addition of thanol as solubilizer, and with acid buffering agents to an d pH of 4.0. Stabilizing and preserving agents may also ptionally be added. Suitable compositions for pulmonary pplication from a conventional metered delivery device may e made up for example as follows:

ueous solutions are prepared comprising (a) 0.5, (b) 1.0 (c) 2.0 mg (R)-ALBUTEROL as the sulphate/ml and adjusted pH ca. 4.0 by the addition of H_2SO_4. Compositions are lled in 2.5ml amounts, comprising 0.5%, 1.0% and 2.0% R)-ALBUTEROL, into plastic ampoules for insertion into a onventional metered device, e.g. for use, in relation to mposition (a) with 2x actuation delivering a total of 0μg (R)-ALBUTEROL 2 to 4x daily, in relation to mposition (b) with 1x actuation delivering a total of 0μg (R)-ALBUTEROL 2 to 4x daily or in relation to mposition (c) with 1x actuation delivering a total of 0μg (R)-ALBUTEROL 1 to 2x daily.

Equivalent compositions may be prepared comprising BRONCHODILATOR ENANTIOMER of any other GROUP 1.3 DRUG, e.g. as hereinbefore referred to, either at conventional unit drug concentration** for administration at 50% conventional dosaging rate or at 50% conventional drug concentration for administration at conventional dosaging rate.

[**For the drug substances ISOETHARINE, METAPROTERENOL, TERBUTALINE, FENOTEROL and CARBUTEROL for example, conventional inhaled doses (per puff) are 350μg; 650μg; 250μg; 200μg; and 100μg racemate respectively, for use in two puffs generally administered 2 to 4 or up to 6x daily.]

In accordance with the foregoing the present invention also provides:

E A pharmaceutical composition comprising a GROUP 1.3 DRUG predominantly in the form of its BRONCHODILATOR ENANTIOMER as active ingredient, together with a pharmaceutically acceptable diluent or carrier therefor.

Pharmaceutical compositions are to be understood as being, in particular, compositions of which the individual components are not only suitable or allowable for therapeutic usage but which are manufactured and processed under conditions of sterility appropriate or required for therapeutic usage.

When the method of the present invention is practiced in conjunction KETOTIFEN therapy, dosages of KETOTIFEN employed will generally be the same or of similar order to KETOTIFEN dosages as conventionally employed for the prophylaxis or management of asthma, that is of the order of 1 to 4mg, preferably 2 or 4mg/day/p.o., suitably administered in 1 or 2mg doses, preferably 1x or 2x daily, or in liquid e.g. syrup form. Suitable oral dosage forms, e.g. 1mg and 2mg

tablets and capsules as well as syrup formulations comprising KETOTIFEN as active ingredient, for use in practicing the present invention are known and commercially available.

Utility of the present invention may also be demonstrated in clinical trials, for example, performed as follows:

CLINICAL TRIAL I

Trial subjects are selected from patients having a clinical history of asthma and demonstrable airway obstruction (e.g. FEV_1 less than predicted from standard tables) that is resolved by inhalation of clinical doses of GROUP 1.3 DRUGS in conventional, racemic form [e.g. of (R,S)-ALBUTEROL]. Subjects also exhibit demonstrable increase in airway reactivity to inhaled histamine or methacholine. Typically, selected subjects are young adults (ca. 15 to 25 years of age) allergic to pollens, animal danders or house dust mite, using inhaled conventional, racemic GROUP 1.3 DRUG therapy intermittently (e.g. according to subjective perception of symptoms), with or without additional anti-asthma therapy such as inhaled steroid, cromoglycate or KETOTIFEN.

Trial subjects are divided into separate groups receving either conventional, racemic GROUP 1.3 DRUG [e.g. (R,S)-ALBUTEROL] at conventional doses of 200μg or BRONCHODILATOR ENANTIOMER of GROUP 1.3 DRUG dosing [e.g. (R)-ALBUTEROL] at 50% doses of 100μg, all doses administered by inhalation regularly, e.g. 2 to 4x daily over a period of 3 to 6 months. Concomitant additional therapy, as mentioned above is maintained where used. Subjects are monitored at monthly intervals during the course of the trial period for airways hyperreactivity, preferably using leukotriene C_4 or D_4 as test spasmogen, e.g. as reported in references already referred to hereinbefore.

Increase in airway hyperreactivity is evidenced in subjects receiving conventional, racemic GROUP 1.3 DRUG. Subjects receiving BRONCHODILATOR ENANTIOMER in contrast exhibit a clearly restricted tendency to increase in hyperreactivity but exhibit equivalent benefit in terms of bronchodilator action during exacerbation. In subjects receiving concomitant KETOTIFEN yet further restricted trend towards increase in hyperreactivity is observed.

CLINICAL TRIAL II

Subjects are selected from patient groups as described for TRIAL I. Subjects receive conventional, racemic GROUP 1.3 DRUG [e.g. (R,S) ALBUTEROL at 200μg by inhalation] or BRONCHODILATOR ENANTIOMER of GROUP 1.3 DRUG [e.g. (R)-ALBUTEROL at 100μg by inhalation]. The alternative therapies are assigned to individual subjects in randomized, double-blind manner. Pulmonary function (e.g. FEV_1) and sensitivity to a test of airway hyperreactivity (e.g. inhaled aerosolised histamine) is determined before drug-administration and after intervals (e.g. of 2 and 5 hours) post drug-administration.

In the case of subjects receiving conventional, racemic GROUP 1.3 DRUG, evident mismatch is recorded between observed drug bronchodilator efficacy and suppression of manifestation of hyperreactivity, such that there is no observed protection from manifestation of hyperreactivity even though substantial bronchodilator response remains evident. In subjects receiving BRONCHODILATOR ENANTIOMER, degree of mismatch is significantly reduced while bronchodilator efficacy is maintained.

CLAIMS

100-7730

1. A selective β_2 sympathomimatic bronchodilator drug predpminantly in the form of its BRONCHODILATOR ENANTIOMER for use in the improved treatment of inflammatory or obstructive airways disease in humans

2. A selective β_2 sympathomimatic bronchodilator drug predominantly in the form of its BRONCHODILATOR ENANTIOMER for use as defined in claim 1, wherein the improved treatment comprises treatment to avoid, ameliorate or restrict occurrence of side effect deleterious to the airways.

3. A selective β_2 sympathomimatic bronchodilator drug predominantly in the form of its BRONCHODILATOR ENANTIOMER for use as defined in claim 1, wherein the improved treatment comprises treatment to avoid, ameliorate or restrict exacerbation of basal disease status or compromise or deterioration of lung functio

4. A selective β_2 sympathomimatic bronchodilator drug predominantly in the form of its BRONCHODILATOR ENANTIOMER for use as defined in any one of claims 1 3, wherein said use comprises use in conjunction with use of Ketotifen.

5. The BRONCHODILATOR ENANTIOMER of a selective β_2 sympathomimatic bronchodilator drug in pure or substantially pure form for use as defined in any one claims 1 to 4.

6. The use of a selective β_2 sympathomimatic bronchodila drug predominantly in the form of its BRONCHODILATOR ENANTIOMER or the use of the BRONCHODILATOR ENANTIOME of a selective β_2 sympathomimatic bronchodilator drug pure or substantially pure form for the preparation o pharmaceutical composition for use in a method of

treatment as defined in any one of claims 1 to 4.

7. A selective β_2 sympathomimatic bronchodilator drug selected from the group consisting of terbutaline, albuterol, fenoterol, hexoprenaline, rimiterol, isoetharine, orciprenaline, reproterol, clenbuterol, procaterol, carbuterol, tolobuterol, pirbuterol, bitolterol, formoterol, bambuterol and salmeterol predominantly in the form of its BRONCHODILATOR ENANTIOMER or the BRONCHODILATOR ENANTIOMER of a selective β_2 sympathomimatic bronchodilator drug selected from the aforesaid group in pure or substantially pure form for use as defined in any one of claims 1 to 4 or 6.

8. A pharmaceutical composition comprising a β_2 sympathomimatic bronchodilator drug predominantly in the form of its BRONCHODILATOR ENANTIOMER or the BRONCHODILATOR ENANTIOMER of a selective β_2 sympathomimatic bronchodilator drug in pure or substantially pure form together with a pharmaceutically acceptable diluent or carrier therefor.

9. A pharmaceutical composition according to claim 8 wherein the β_2 sympathomimatic bronchodilator drug is selected from the group defined in claim 7.

10. Ketotifen for use in the preparation of a pharmaceutical composition for use in further improving use as defined in any one of claims 1 to 3 of a selective β_2 sympathomimatic bronchodilator drug in the form of its BRONCHODILATOR ENANTIOMER or of the BRONCHODILATOR ENANTIOMER of a selective β_2 sympathomimatic bronchodilator drug in pure or substantially pure form.

PATENT NO.

ORIGINAL CLASSIFICATION

CLASS: 514 | 649

APPLICATION SERIAL NUMBER: 09/063,551

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)			
514	826			

APPLICANT'S NAME (PLEASE PRINT): Timothy J. Barberich et al

IF REISSUE, ORIGINAL PATENT NUMBER

INTERNATIONAL CLASSIFICATION (IPC)

A	61	K		31/135	

GROUP ART UNIT: 1614

ASSISTANT EXAMINER (PLEASE STAMP OR PRINT FULL NAME)

PRIMARY EXAMINER (PLEASE STAMP OR PRINT FULL NAME): Raymond J. Henley III

PTO 270 (REV. 5-91)

ISSUE CLASSIFICATION SLIP

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

PATENT APPLICATION FEE DETERMINATION RECORD

Effective October 1, 1997

Application or Docket Number: 09/063,551

CLAIMS AS FILED - PART I

	(Column 1) NUMBER FILED		(Column 2) NUMBER EXTRA	SMALL ENTITY TYPE ☐ RATE	FEE	OR	OTHER THAN SMALL ENTITY RATE	FEE
FOR								
BASIC FEE					395.00	OR		790.00
TOTAL CLAIMS	10	minus 20 =	*	x$11=		OR	x$22=	
INDEPENDENT CLAIMS	2	minus 3 =	*	x41=		OR	x82=	
MULTIPLE DEPENDENT CLAIM PRESENT				+135=		OR	+270=	
				TOTAL		OR	TOTAL	

* If the difference in column 1 is less than zero, enter "0" in column 2

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE	ADDI-TIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	ADDI-TIONAL FEE
Total	*	Minus	**	=	x$11=		OR	x$22=	
Independent	*	Minus	***	=	x41=		OR	x82=	
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					+135=		OR	+270=	
					TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE	ADDI-TIONAL FEE	OR	RATE	ADDI-TIONAL FEE
Total	*	Minus	**	=	x$11=		OR	x$22=	
Independent	*	Minus	***	=	x41=		OR	x82=	
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					+135=		OR	+270=	
					TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE	ADDI-TIONAL FEE	OR	RATE	ADDI-TIONAL FEE
Total	*	Minus	**	=	x$11=		OR	x$22=	
Independent	*	Minus	***	=	x41=		OR	x82=	
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM					+135=		OR	+270=	
					TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
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APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
09/063,551	04/21/98	010	HENLEY III, R. 1614	06/24/98

...st Named ...plicant: BARBERICH, TIMOTHY J.

...E OF ...NTION: METHOD FOR INDUCING BRONCHODILATION USING OPTICALLY PURE R(-)ALBUTEROL (AS AMENDED)

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1 0701.027F	514-649.000	F87	UTILITY	NO	$660.00 ~~$660.00~~	09/24/9

Change of correspondence address or indication of "Fee Address" (37 CFR 1.363). Use of PTO form(s) and Customer Number are recommended, but not required.

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

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1 Heslin & Rothenberg, P.
2
3

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(A) NAME OF ASSIGNEE: Sepracor, Inc.

(B) RESIDENCE: (CITY & STATE OR COUNTRY) Marlborough, MA

Please check the appropriate assignee category indicated below (will not be printed on the patent)
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United States Patent [19]

Barberich et al.

[11] Patent Number: 5,844,002

[45] Date of Patent: Dec. 1, 1998

[54] METHOD FOR INDUCING BRONCHODILATION USING OPTICALLY PURE R(–) ALBUTEROL

[75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of Mass.

[73] Assignee: Sepracor, Inc., Marlborough, Mass.

[21] Appl. No.: 63,551

[22] Filed: Apr. 21, 1998

Related U.S. Application Data

[63] Continuation of Ser. No. 691,604, Aug. 15, 1996, Pat. No. 5,760,090, which is a continuation of Ser. No. 335,480, Nov. 7, 1994, Pat. No. 5,547,994, which is a continuation of Ser. No. 163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 451,262, Jan. 5, 1990, abandoned.

[51] Int. Cl.[6] A61K 31/135

[52] U.S. Cl. 514/649; 514/826

[58] Field of Search 514/649, 826

[56] References Cited

U.S. PATENT DOCUMENTS

5,362,755	11/1994	Barberich et al.	514/649
5,547,994	8/1996	Barberich et al.	514/649
5,760,090	6/1998	Barberich et al.	514/649

FOREIGN PATENT DOCUMENTS

2128258	of 1983	Germany .
1298494	of 1971	United Kingdom .
2 255 503	of 1992	United Kingdom .

OTHER PUBLICATIONS

Tan et al. "Stereoselective Disposition of Salbutamol Enantiomers . . . " *Clin. Chem.* 33, 1026 (1987).

Brittain et al. "Some observations on the β-adrenoceptor agonist . . . " *Br. J. Pharmac.* 43, 144–147 (1973).

Hartley et al. "Absolute Configuration of the Optical Isomers of Salbutamol" *J. Med. Chem.* 12, 995 (1971).

Hawkins et al. "Relative Potency of (–)- and (±)-Salbutamol on Guinea Pig . . . " *J. Med. Chem.* 16, 856–857 (1973).

Buckner et al. "Studies on the Effects of Enantiomers of Sotrexanel, Trimetoquinol . . . " *J. Pharm. Exp. Ther.* 189, 616–625 (1974).

Passowicz-Muszyńska E. "Effect on beta adrenergic receptors of theophylaxis . . . " *Index Medicus* 91:164287.

Paalwels "Effect of corticosteroids on the action of sympathomimetics" *Index Medicus* 86:051970.

Chapman et al. "An anomalous effect of salbutamol in sensitised guinea pigs" *Brit. J. Pharmacol* 99, 66P (1990).

Morley et al. "Effects of (+) and racemic salbutamol on airway responses in the guinea pig" *Brit. J. Pharmacol.* 104, 295P (1991).

Chapman et al. "Racemic mixtures, at root of worsening symptoms? Active enantiomers . . . " *TIPS* 13, 231–232 (1992).

Mutlari et al. "Comparison of acute bronchodilator effects of oral salbutamol, . . . " *Chem. Abstr.* 89: 123259n (1978).

Primary Examiner—Raymond Henley, III
Attorney, Agent, or Firm—Heslin & Rothenberg, P.C.

[57] ABSTRACT

The optically pure R(–) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(–) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

10 Claims, No Drawings

METHOD FOR INDUCING BRONCHODILATION USING OPTICALLY PURE R(-) ALBUTEROL

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 08/691,504, filed Aug. 15, 1996, now U.S. Pat. No. 5,760,090, which is a continuation of application Ser. No. 08/335,480, filed Nov. 7, 1994, now U.S. Pat. No. 5,547,994, which is a continuation of application Ser. No. 08/163,581, filed Dec. 7, 1993 now U.S. Pat. No. 5,362,755, which is a continuation of application Ser. No. 07/896,725, filed Jun. 9, 1992 now abandoned, which was a continuation of application Ser. No. 07/461,262, filed Jan. 5, 1990, now abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(-) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(-) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the broncho-dilation activity of the R(-) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(-) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(-) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α[(tert-butylamino)methyl] -4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or clathrate. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(-) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(-) isomer of albuterol is administered to an individual who has asthma. For example, R(-) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(-) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(-) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(-) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(-) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(-) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(-) albuterol. The two (or more)

drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalant form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

Equivalents

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of inducing bronchodilation or providing relief of bronchospasm, comprising administering to an individual a quantity of optically pure R-(−) albuterol sufficient to induce said bronchodilation.

2. A method according to claim 1, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

3. A method according to claim 1, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

4. A method according to claim 1, wherein the optically pure R(−) albuterol is administered by inhalation.

5. A method according to claim 4, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

6. A method according to claim 1, wherein the optically pure R(−) albuterol is administered orally.

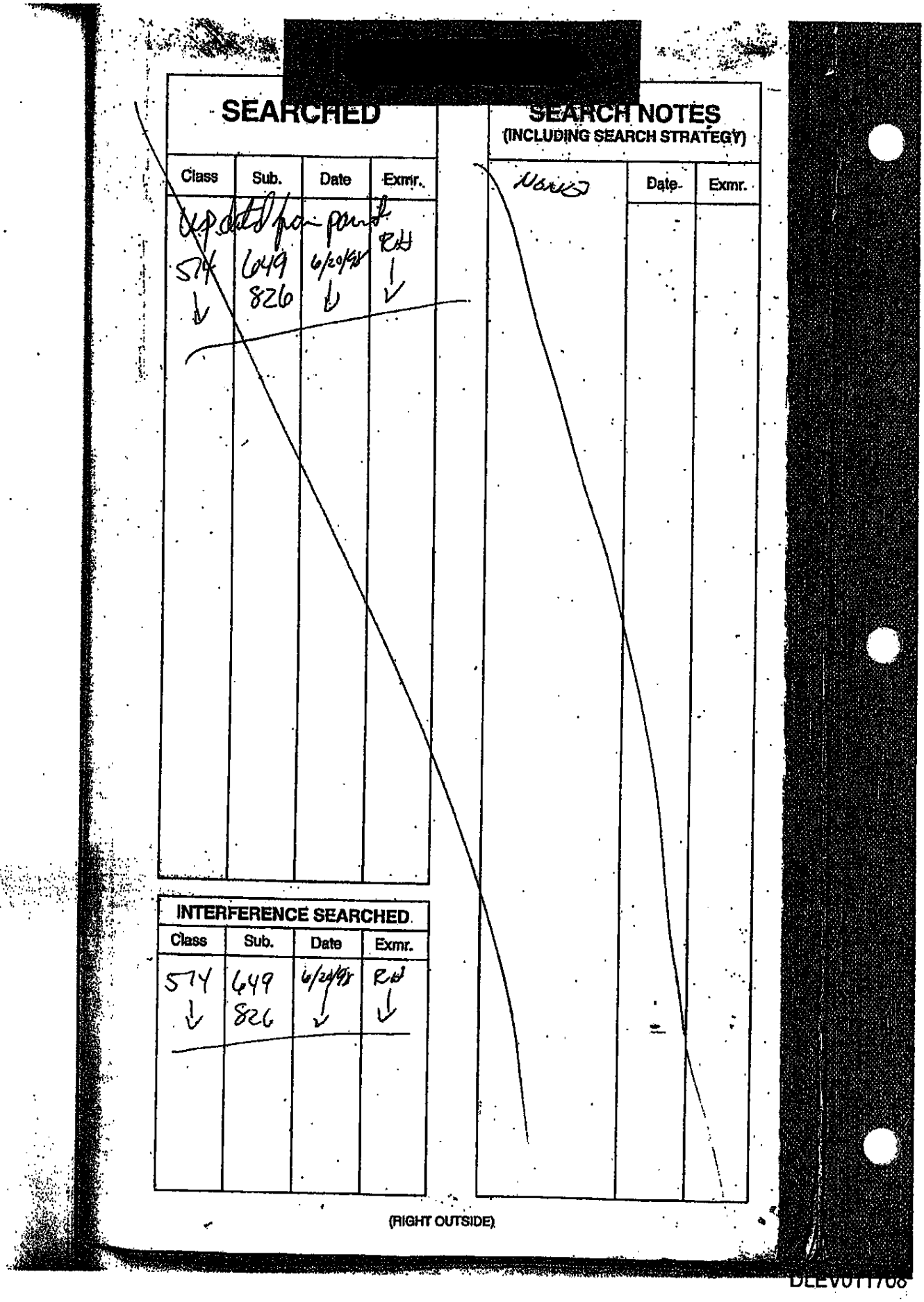
7. A method according to claim 6, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

8. A method according to claim 6, wherein the optically pure R(−) albuterol is administered as a syrup.

9. A method according to claim 7, wherein the optically pure R(−) albuterol is administered as a syrup.

10. A method of inducing bronchodilation or providing relief of bronchospasm while reducing the concomitant liability of adverse effects associated with racemic albuterol, comprising administering to an individual a quantity of optically pure R-(−) albuterol sufficient to induce said bronchodilation while simultaneously reducing said adverse effects.

* * * * *



SEARCHED

Class	Sub.	Date	Exmr.
updated for pmt			
514 ↓	649 826	6/20/98 ↓	RH ↓

SEARCH NOTES
(INCLUDING SEARCH STRATEGY)

	Date	Exmr.
Words		

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.
514 ↓	649 826 ↓	6/24/98 ↓	RH ↓

(RIGHT OUTSIDE)

DLEV011708

ISSUE SLIP STAPLE AREA (for additional cross references)

POSITION	INITIALS	ID NO.	DATE
DETERMINATION	W	7534	04-2098
P.E. CLASSIFIER		16	42998
RMALITY REVIEW	EF	59584	5/6/98

INDEX OF CLAIMS

✓ ..... Rejected
= ..... Allowed
— (Through numeral) Canceled
÷ ..... Restricted
N ..... Non-elected
I ..... Interference
A ..... Appeal
O ..... Objected

Date	Claim	Date	Claim	Date
	Final / Original		Final / Original	
	51		101	
	52		102	
	53		103	
	54		104	
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If more than 150 claims or 10 actions staple additional sheet here

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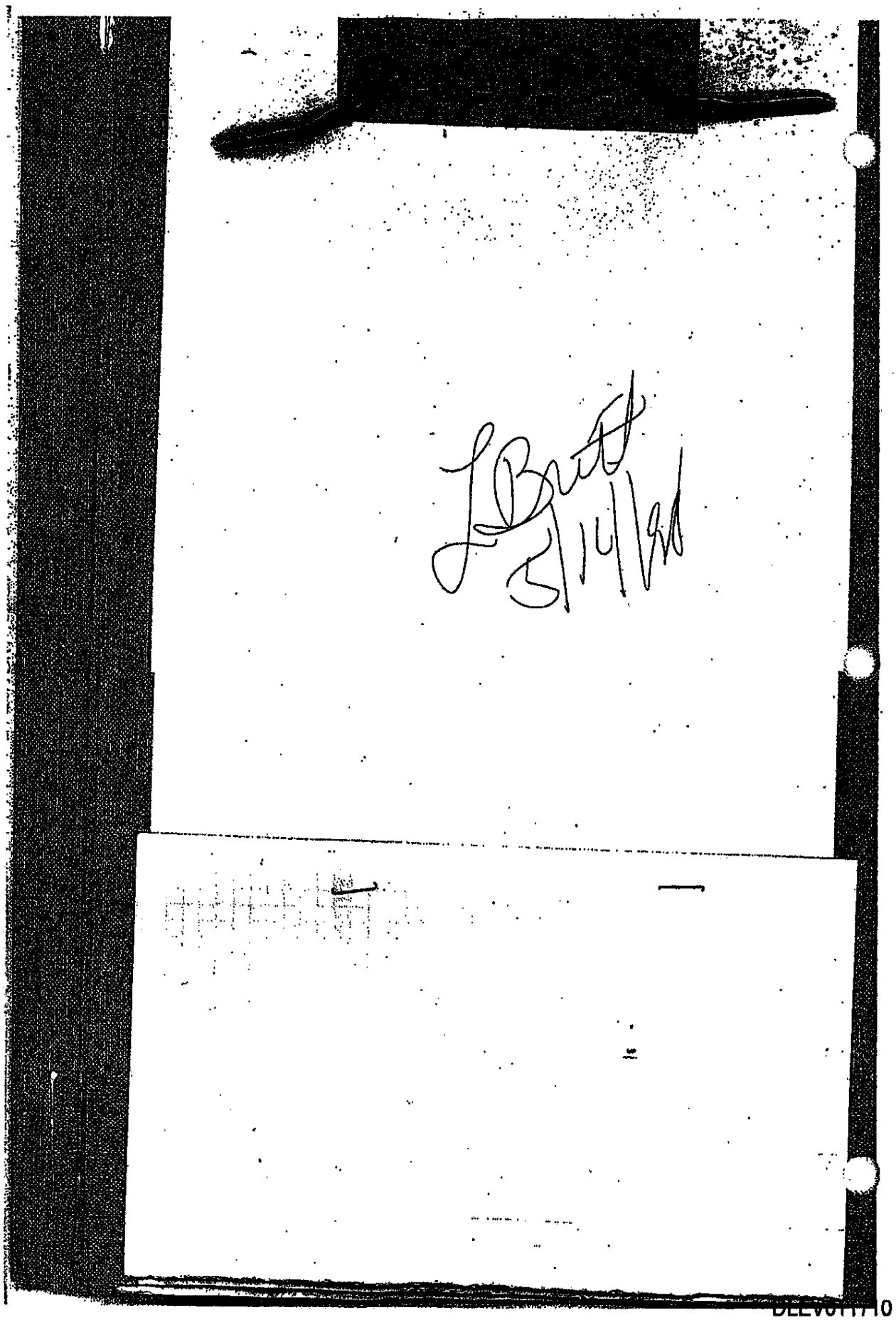

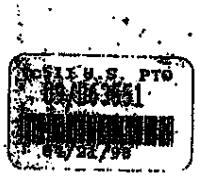

PATENT APPLICATION

09063551

APR 29 9827

INITIALS

CONTENTS

	Date received (Incl. C. of M.) or Date Mailed		Date received (Incl. C. of M.) or Date Mailed
1. Application ____ papers.		42.	
2.		43.	
3. Ltr Amend A	4-27-98	44.	
4. Terminal Disc.	4-27-98	45.	
5. Notice of Allowability	8/24/98	46.	
6. PTO GRANT AUG 31 1998		47.	
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